

## 1. Name of the Medicinal Product

- (a) Product Name : Zespar-200 Tablets (Sparfloxacin Tablets 200 mg)  
(b) Strength : 200 mg  
(c) Pharmaceutical Dosage Form : Tablets

## 2. Quality and Quantitative Composition

(a) Qualitative Declaration, the active substance should be declared by its recommended INN. Accompanied by its salt or hydrate form if relevant.

### Composition:

Each filmcoated tablet contains:  
Sparfloxacin 200 mg

(b) Quantitative Declaration, the quantity of the active substance must be expressed per dosage unit

Sr. No.	Name of the Materials	Specification	Label Claim	Quantity (mg/Tablet)	Active/ Inactive
1	Sparfloxacin	In-House	200 mg	200.0 mg	Active

**3. Pharmaceutical Form Visual description of the appearance of the product (colour, markings, etc.) e.g.:** Yellow colour, round biconvex shape and film coated tablet. One side smooth and other side scored.

## 4. Clinical Particulars

### 4.1 Therapeutic Indications:

Zespar-200 Tablets is indicated in the treatment of radiologically confirmed community acquired pneumonia which has failed to respond to conventional therapy:

- either caused by pneumococci, highly resistant to penicillin ( $MIC > 2 \text{ mg/l}$ ) and other antimicrobials,
- or occurring in an epidemiological environment indicating that the risk of such a multiresistant strain is high.

### 4.2 Posology and method of administration:

*In patients with normal renal function:*

- 400 mg as a single dose on the first day,
- then 200 mg/day in a single daily dose.

The duration of maintenance therapy is 10 days on average, to a maximum of 14 days. No benefit is to be expected by increasing the daily dose.

*In patients with renal failure:*

No studies have been performed in patients with moderate renal impairment (creatinine clearance  $\geq 30 \text{ ml/min}$ ). Due to the small rate of urinary elimination (10 %) no dosage adaptation is necessary.

Nevertheless, caution should be observed in this group of patients.

*In severe renal failure (creatinine clearance < 30 ml/min), the following dosage schedule should be observed:*

- 400 mg loading dose the first day
- then 200 mg the third day
- then every 48 hours, for a maximum of 14 days.

Safe administration in haemodialysis or peritoneal dialysis patients has not been established. Therefore, administration of sparfloxacin to these patients is not recommended.

*In patients with hepatic failure*

- Hepatic impairment without cholestasis: no dosage modification is required (see "Pharmacokinetic properties")
- No data are available on patients with serious hepatic insufficiency.

#### **Method of administration:**

Zespar-200 Tablets can be taken by oral route only.

#### **4.3 Contraindications:**

Hypersensitivity to the active substance or to any of the excipients

#### **4.4 Special warning and precautions for use:**

*Phototoxicity:*

Phototoxic reactions are common and are characterized by redness, swelling and blisters. These reactions are sometimes severe, patients may develop second degree burns and may require hospitalisation. The frequency of these reactions is higher than with other fluoroquinolones.

Phototoxicity can occur in cloudy weather or even in the absence of direct exposure to the sun.

Consequently, patients should be advised to avoid exposure to the sun, bright light and UV rays throughout the entire duration of treatment and for 5 days after treatment is stopped. Patients must be instructed to discontinue sparfloxacin therapy at the first sign of symptoms of phototoxicity and to avoid further exposure to the sun, bright light or UV rays for the next 5 days.

Recovery from phototoxicity may be slow and recurrence may occur even several weeks after withdrawal of sparfloxacin.

*Increase in the Q-T interval:*

Increases in the Q-Tc interval have been observed in healthy volunteers treated with sparfloxacin, a mean maximum increase of 19 msec was observed at the recommended dosage of 400/200 mg. In clinical trials involving 813 patients, the average prolongation was around 3%, and 1.2% of patients developed Q-Tc intervals greater than 500 msec (prolongation of 100 msec in 0.3%), but with no arrhythmic effects.

As a consequence, the use of sparfloxacin in patients with known Q-Tc prolongation congenital or acquired (e.g. acute myocardial infarction) and the concomitant use of drugs known to produce an increase in the Q-Tc interval and/or torsades de pointes is inadvisable: e.g. quinine, chloroquine, erythromycin, terfenadine, astemizole, probucol, halofantrine, pentamidine, vincamine, class Ia antiarrhythmic agents (e.g. quinidine, procainamide, disopyramide), class III anti-arrhythmic agents

(e.g. bretylium), some tricyclic antidepressants, some neuroleptics (e.g. sultopride, phenothiazines) (see "Interaction with other medicinal products and other forms of interaction").

Sparfloxacin is contra-indicated in patients receiving amiodarone, sotalol or bepridil

*Conditions that predispose to the development of torsades de pointes:*

-Hypokalaemia: patients with a known history of hypokalaemia including that caused by concomitant medications (see "Interaction with other medicinal products and other forms of interaction") should have their potassium concentrations corrected before commencing treatment with sparfloxacin.

-Bradycardia of any cause

-Atrio-ventricular conduction defects

-Use with caution and under close surveillance in case of cardiac arrhythmias in particular in case of bradyarrhythmias.

*Tendinitis:*

Tendinitis and/or tendon rupture (particularly affecting the Achilles tendon) occurs in association with quinolone antibiotics. Such reactions have particularly been noted in older patients and those on corticosteroids. At the first sign of pain or inflammation, patients should discontinue sparfloxacin and rest the affected limb. If symptoms involve the Achilles tendon, measures should be taken to ensure that rupture of both does not occur (e.g. both are supported with a suitable brace or heelpiece).

*Mycobacteria:*

In cases of suspected tuberculosis, the potential activity of sparfloxacin against mycobacteria should be taken into account. Sparfloxacin may produce false-negative culture results for mycobacteria.

#### **4.5 Interaction with other medicinal products and other forms of interactions:**

*Contra-indicated concomitant medications:*

- Amiodarone, sotalol and bepridil: risk of torsades de pointes due to prolongation of the Q-T interval (additive electrophysiologic effects).

*Inadvisable concomitant medications:*

- Drugs that produce QT prolongation and/or torsades de pointes:

- antiarrhythmic agents: bretylium, disopyramide, procainamide, quinidine.

- other drugs: astemizole, erythromycin, quinine, chloroquine, halofantrine, pentamidine, probucol, terfenadine, vincamine, some tricyclic antidepressants, some neuroleptics (e.g. sultopride, phenothiazines): risk of torsades de pointes due to prolongation of the Q-Tc interval (additive electrophysiologic effects). Close clinical and electrocardiographic monitoring is required if it is considered essential to use with any of these drugs.

*Concomitant medications requiring precautions for use:*

- Iron salts (oral use): reduction of the bioavailability of sparfloxacin due to chelation and due to a nonspecific effect on the absorption capacity of the gastrointestinal tract. Iron salts should be taken after sparfloxacin (at least 2 hours later if possible).

- Salts, oxides and hydroxides of magnesium, aluminium and calcium (antacids): reduction of the gastrointestinal absorption of sparfloxacin. Antacids should not be taken at the same time as sparfloxacin (at least 4 hours apart if possible).

- Zinc salts (oral use), described for zinc salts at doses > 30 mg/d: reduction of the gastrointestinal absorption of sparfloxacin. Zinc salts should be taken after sparfloxacin (at least 2 hours later if possible).
- Hypokalaemia caused by drugs such as non-potassium sparing diuretics, stimulant laxatives, amphotericin B (IV.), cortico-steroids and tetracosaccharide may pre-dispose to the development of torsades de pointes. Potassium levels should be within the normal range before treatment with sparfloxacin is started. Hypokalaemia should not be allowed to develop during sparfloxacin use.
- Bradycardia caused by drugs such as digoxin and beta-blockers may predispose to the development of torsades de pointes. If it is considered essential that sparfloxacin is used in conjunction with therapy associated with bradycardia, then close electrocardiographic monitoring should be carried out.

*Concomitant medications to be taken into account*

- NSAIDs and theophylline: quinolone antibiotics can reduce the seizure threshold particularly in association with drugs such as NSAIDs and theophylline.

**4.6 Pregnancy and lactation:**

*Pregnancy:*

There are no human studies of the use of sparfloxacin in pregnancy and lactation. However, reproduction studies performed in rats, rabbits and monkeys dosed orally did not reveal any evidence of impairment of fertility and peri/post natal development. When administered to rats during organogenesis, sparfloxacin demonstrates a dose-related increase in the incidence of ventricular septal defects (this effect was not observed in primate studies). In common with other quinolones, sparfloxacin has demonstrated arthrotoxic potential in growing animals. Women of childbearing potential should be advised to avoid becoming pregnant during sparfloxacin therapy and sparfloxacin should not be prescribed to pregnant women.

*Lactation:*

Sparfloxacin is secreted in breast milk. Because of the potential for serious adverse reactions in nursing infants, it is recommended that women be advised not to breast feed during sparfloxacin therapy.

**4.7 Effects on ability to drive and use machine:**

Zespar-200 Tablets (200 mg) has no influence on the ability to drive and use machines.

**4.8 Undesirable effects:**

*Phototoxicity* including manifestations of sunburn, erythema and severe bullous lesions. Recurrence of the symptoms after a new sun exposure, several weeks after the end of the treatment, has been sometimes observed.

*Skin reactions:* rash, pruritus, swelling, blisters.

*Musculoskeletal:* muscle or joint pain, tendinitis, ruptured tendon (see “Contra-indications” and “Special Warnings and Special Precautions for use”).

*Cardiovascular:* rare cardiac rhythm disorders including torsades de pointes, arrhythmia, bradycardia, tachycardia and ventricular tachycardia (see “Contraindications” and “Interaction with other medicinal products and other forms of interaction”).

*Digestive disorders:* nausea, vomiting, diarrhoea, abdominal pain, gastralgia.

*Nervous System:* tremor, feeling drunk, paraesthesia, sensory disturbance, headache and vertigo.

*Psychiatric disorders:* hallucinations, sleep disorders at the beginning of treatment.

*Body as a whole:* rare cases of hypersensitivity, including urticaria, angioedema, anaphylactic shock and Quincke's oedema.

*Hematologic System:* isolated cases of thrombocytopenia and rare cases of thrombocytopenic purpura.

*Vision disorders:* Conjunctivitis and uveitis.

#### **4.9 Overdose:**

If overdose occurs the patient should be monitored for evidence of toxicity and standard supportive treatment applied as necessary

## 5. Pharmacological Properties

### 5.1 Pharmacodynamic Properties:

**Pharmacotherapeutic group:** Antibiotic from the quinolone family

ATC code: J01MA09

Sparfloxacin, an aminodifluoroquinolone, is a synthetic antibiotic belonging to the quinolone family. Sparfloxacin exhibits a spectrum of activity which is related to the therapeutic indication and focused on *S.pneumoniae*.

However, other bacterial species usually susceptible to sparfloxacin can be associated in community acquired pneumonia. In such a situation, no combination therapy is needed because of a spectrum of activity which includes all respiratory pathogens.

- Susceptible species (MIC  $\leq$  1 mg/l):

*Streptococcus pneumoniae* including those strains resistant to beta-lactam and macrolide antibiotics

*Streptococcus* of groups A, C and G

Methicillin-susceptible

*Staphylococcus*

*Haemophilus influenzae* including beta-lactamase producing strains

*Moraxella catarrhalis*

*Mycoplasma pneumoniae*, *Chlamydia psittaci* and *pneumoniae Legionella*

- Resistant species (MIC  $>$  2 mg/l):

Methicillin-resistant *Staphylococcus*

### 5.2 Pharmacokinetic Properties:

#### Absorption

The absorption of sparfloxacin is rapid with peak serum concentrations achieved 3 to 5 hours after the first dose. Oral absorption is not modified by the presence of food. Steady-state plasma concentrations are achieved on the first day due to the loading dose that is double the daily dose.

Dosing regimen	Day 1		Steady state	
	Cmax $\mu$ g/ml	Cmin $\mu$ g/ml	Cmax $\mu$ g/ml	Cmin $\mu$ g/ml
400 mg*/200 mg**	1.7	0.6	1.4	0.5

\* Loading dose

\*\* Daily dose

#### Distribution:

After a loading dose of 400 mg, the concentrations found in the extravascular fluid are equivalent to plasma concentrations. In bronchopulmonary tissues, concentrations reached are greater than the MIC of the bacterial species susceptible to sparfloxacin: 10  $\mu$ g/g in pulmonary parenchyma, 16.7  $\mu$ g/ml in alveolar surfactant and 2-5  $\mu$ g/g in bronchial mucosa.

Sparfloxacin concentrates preferentially in macrophages, in which concentrations of 40-50  $\mu$ g/g are reached.

Plasma protein binding is 45 %.

*Metabolism:*

Sparfloxacin is metabolized in the liver to an inactive glucuronide conjugate. Metabolism does not depend on cytochrome mediated oxidation, in particular the cytochrome P450 system.

*Elimination:*

The terminal plasma elimination half-life is approximately 20 hours. Excretion is both fecal and urinary: two-thirds is excreted in the feces as unchanged sparfloxacin, one-third is eliminated in the urine as unchanged sparfloxacin and as the glucuronide conjugate.

Biliary excretion, mainly as the glucuronide conjugate, accounts for 10-20 % of the administered dose.

*Special Populations:*

Patients with renal impairment: In patients with renal impairment (creatinine clearance < 30 ml/min), the elimination half-life of sparfloxacin is 35-40 hours due to partial hydrolysis of the glucuronide conjugate. The accumulation of the glucuronide conjugate is observed in these patients.

Patients with hepatic impairment: The elimination half-life is unchanged in patients with hepatic impairment without cholestasis.

Elderly: The pharmacokinetic properties of sparfloxacin are not modified in the elderly.

### **5.3 Preclinical Safety Data:**

Sparfloxacin exhibits the toxicity profile as following:

- hepatotoxicity based on an increase in hepatic enzymes (e.g. aspartaminotransferase) and a cytologic alteration of the hepatocytes, notably vacuolisation and multifocal or single cell liver necrosis;
- nephrotoxicity, notably glomerulo-nephritis and interstitial nephritis;
- cardiotoxicity with a pronounced prolongation of the QT interval, occurred already in doses close to human dosage;
- arthrotoxicity;
- phototoxicity ;

Under simultaneous U.V. exposure, sparfloxacin can exhibit mutagenic properties and carcinogenetic effects.

Reproductive toxicity studies detected anomalies such as ventricular septum defect in young rats, but these effects were not observed in young monkeys.

## 6. Pharmaceutical Particulars

### 6.1 List of Excipients:

Sr. No.	Name of the Materials
1	Lactose
2	Maize Starch
3	Methylparaben Sodium
4	Gelatin
5	Magnesium Stearate
6	Purified Talc
7	Sodium Starch Glycolate
8	Colloidal Silicon Dioxide
9	Purified water
10	Colour coat
11	Colour Tartrazine

### 6.2 Incompatibilities:

Not applicable

### 6.3 Shelf life:

36 Months

### 6.4 Special precautions for storage:

Store in cool, dark & dry palce.

Keep Out of the Reach of Children.

### 6.5 Nature and contents of container:

1 x10 Tablets Alu-Alu Blister pack

### 6.6 Instructions for use and handling

No special requirements.

## 7. Applicant/Manufacturer

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